REMARKS

Specification

The Specification has been amended to capitalize various trademarks used in the application and to correct a typographical error. No new matter has been added.

Claims

Claim 38 has been added. No new matter has been added. Claims 28-38 are currently pending in this application.

Obviousness Type Double Patenting

Claims 28-37 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-7 and 10 of U.S. Patent No. 6,670,183. As recognized by the examiner, the claims of the '183 Patent relate to in vitro or ex vivo administration of a GP88 antisense oligonucleotide. Applicant notes that the terms in vitro and ex vivo, both relate to an environment outside a living organism. The claims of the present application, however, are not so limited and relate to in vivo methods. Thus, the present claims are not merely obvious variations of claims 5-7 and 10 of U.S. Patent No. 6,670,183. For at least this reason, Applicant respectfully requests withdrawal of this rejection.

35 U.S.C. §112, Second Paragraph

Claims 28-37 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The examiner states that the term "GP88" is not clearly defined since abbreviations often have more than one meaning. Applicants respectfully disagree that the term "GP88" as used in the present claims is unclear and note that the Office Action does not indicate that the term "GP88" as used herein, in fact, has multiple meanings.

To further prosecution, however, the claims have been amended to include the term "PC Cell Derived Growth Factor" in place of GP88. These amendments do not change the scope of any claims.

35 U.S.C. § 112, First Paragraph

Claims 28-37 stand rejected under 35 U.S.C. § 112, first paragraph. The examiner notes that the specification is enabling for a method of inhibiting the growth of a tumor cell and method of inhibiting the protein expression of GP88 in a cell by the subcutaneous injection of GP88 antisense targeted to SEQ ID NO:16 using primer pairs SEQ ID NO:12 and SEQ ID NO:14. The examiner, however, states that the specification does not reasonably enable a method of inhibiting the growth of a tumor cell or inhibiting the protein expression of GP88 in a cell, comprising any route of administration of any antisense targeted to GP88, wherein the antisense inhibits the growth of tumor cells or the expression of GP88. This rejection is respectfully traversed.

The examiner alleges that antisense therapy is unpredictable and requires undue experimentation to identify antisense sequences. Specifically, the examiner states that because binding of an oligonucleotide to target RNA depends on the base composition and sequence of the target RNA, the feasibility of antisense therapy for one antisense sequence does not demonstrate the feasibility of antisense therapy for a different antisense oligonucleotide. Office Action at 8. The examiner further states that this position is supported by Zang et al. Specifically, the examiner states that Zang et al. show that two antisense, ASII1 and ASII18 were effective, while antisense, ASII15 was not effective. Office Action at 8.

It has been well know to those of ordinary skill in the art that that binding of one nucleotide sequence to another depends on the complimentarity of between the nucleotide sequences. Complimentarity, in turn, depends on the base composition and sequence. Because it is known that complimentary sequences tend to bind to one another, those of ordinary skill in the art are able to determine potentially effective antisense sequences based on a known target sequence.

The present claims are not so broad as to cover any oligonucleotide without regard to its base composition or sequence, but are limited to "a PC Cell Derived Growth Factor antisense oligonucleotide." The specification provides ample guidance in determining and selecting effective antisense sequences:

> Antisense oligonucleotides having a size of 15-30 bases in length and with sequences hybridizable to any of several portions of the target GP88 cDNA, including the coding sequence, 3' or 5' untranslated regions, or other intronic sequences, or to GP88 mRNA, are preferred. Sequences for the antisense oligonucleotides to GP88 are preferably selected as being the ones that have the most potent antisense effects. Factors that govern a target site for the antisense oligonucleotide sequence are related to the length of the oligonucleotide, binding affinity, and accessibility of the target sequence. Sequences may be screened *in vitro* for potency of their antisense activity by measuring inhibition of GP88 protein translation and GP88 related phenotype, e.g., inhibition of cell proliferation in cells in culture. In general it is known that most regions of the RNA (5' and 3' untranslated regions, AUG initiation, coding, splice junctions and introns) can be targeted using antisense oligonucleotides.

Specification at paragraph [0116] (citations omitted). Such screening techniques are routinely used in the art and are not considered undue experimentation. See MPEP § 2164.01.

Moreover, the examiner's interpretation of Zang et al. is incorrect. Zang et al. clearly show that the ASII5 antisense is effective at inhibiting tumor growth, but less effective than ASII1 and ASII18. Each of the antisense transfectants showed reduced tumor growth over the control transfectants. See Zang et al. at pages 14205-6, Figure 7.

The examiner further states that even to date, antisense oligonucleotides are not enabled for therapeutic purposes. This is entirely incorrect. "During the past decade or more, substantial progress has been made in developing antisense pharmacology. . . . Antisense technology has proven of great value in gene fictionalization and target validation. With one drug marketed, Vitravene, and approximately 20 antisense drugs in clinical development, it appears that antisense drugs may prove of value in the treatment of a wide range of diseases." Crooke, S. T., Antisense strategies, *Current Molecular Medicine*, vol. 4(5):465-87 (2004). "The last few years have seen a rapid increase in the number of antisense molecules progressing past Phase I, II and III clinical trials." boul-Fadl, T., Antisense oligonucleotides: the state of the art, *Current Medicinal Chemistry*, 12(19):2193-214 (2005). Thus, it is well recognized that antisense oligonucleotides are successfully used for therapeutic purposes.

The examiner also contends that it is well established in the art that there is a significant level of unpredictability regarding the delivery of oligonucleotide-based therapies. Therefore, the examiner concludes that because the present specification provides a working example of local delivery by subcutaneous injection, only subcutaneous injection of GP88 antisense is enabled. Applicant respectfully disagrees.

At the time the application was filed, those of ordinary skill in the art would have appreciated that a wide variety of delivery routes were available for oligonucleotides. "[A]n ever expanding body of *in vivo* animal experiments has shown

that parenterally delivered phosphorothioate [oligonucleotides] (PS-ODNs) can be effectively absorbed by animals even in simple saline solutions. These data quickly led to the conclusion that delivery is not a problem in the application of [oligonucleotides] *in vivo*." Wang et al., Progress in the Delivery of Therapeutic Oligonucleotides: Organ/Cellular Distribution and Targeted Delivery of Oligonucleotides In Vivo, *Antisense and Nucleic Acid Drug Development* 13:169-189 (June 2003). See also, Brysch et al., Design and Application of Antisense Oligonucleotides in Cell Culture, in Vivo, and as Therapeutic Agents, *Cellular and Molecular Neurobiology*, vol. 14, no. 5 (1994). Wang et al. further describe well known delivery routes, for example, systemic and local delivery routes, including oral, topical, and intravenous, among others. If . . . the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. MPEP § 2164.01(c) (citing In re Johnson, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); In re Hitchings, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965); In re Brana, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).

Even Nielsen, relied upon by the Examiner to show that delivery is unpredictable, acknowledges that in vivo delivery methods are effective for siRNA and other phosphate-based (anionic) antisense agents. Nielsen, The Last Hurdle?, *Gene Therapy*, 12, 956-957, col. 1 (2005). Nielsen presents only a skepticism regarding what Nielsen terms a "simple" and "general" approach to systemic delivery of genetic therapy agents, and does not show that delivery of oligonucleotides is ineffective or unpredictable. In fact, many of the studies Nielsen cites show successful delivery of genetic therapy agents.

Moreover, in addition to providing the working example noted by the examiner, the specification provides ample guidance for a variety of effective delivery methods. Specifically, the specification notes that the preferred GP88 antisense oligonucleotides are "those oligonucleotides which are stable, have a high resilience to nucleases (enzymes that could potentially degrade oligonucleotides), possess suitable pharmacokinetics to allow them to traffic to disease tissue at non-toxic doses, and have the ability to cross through plasma membranes." Specification at paragraph [0117]. The specification notes that phosphorothioate antisense oligonucleotides, peptide nucleic acids, and other stabilized forms of oligonucleotides are effective for delivery. Further, the specification notes that delivery mediated by cationic liposomes, by retroviral vectors and direct delivery are efficient. Specification at paragraphs [0118] and [0119] (citations omitted). As indicated in Wang et al., systemic and local delivery of phosphorothioate antisense oligonucleotides, was known to be effective at the time the application was filed.

Therefore, one of ordinary skill in the art, based on the guidance provided by the present specification, would have been able to practice the invention as recited by the present claims at the time this application was filed. For at least these reasons, the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. If the Examiner should believe that anything further may be required to place this application in even better form for allowance, she is cordially invited to telephone the undersigned attorneys for Applicant.

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Respectfully submitted,

By _____

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